REMARKS

I. Status of the claims

Claims 1, 2, 6-9, and 13-21 are pending. Applicants have added claim 21 to recite that the aminoalkylmethacrylate copolymer is a copolymer of methyl methacrylate, butyl methacrylate and dimethylaminoethyl methacrylate (see specification at page 8, lines 23-28). Applicants have deleted the phrase "or polyvinyl acetal diethylaminoacetate" from claim 1. Accordingly, Applicants introduce no impermissible new matter, and they request entry of this amendment.

II. Summary of the invention

The present invention relates to a preparation, particularly in powder form, that comprises a medicine of high molecular weight and a cationic polymer such as aminoalkylmethacrylate copolymer, which can be administered to an individual through their mucosa. Aminoalkylmethacrylate copolymers improve the absorption of the high molecular weight medicines through an individual's mucosa, such as their nasal mucosa.

III. The present claims are not anticipated by WO 93/24149

Applicants acknowledge the Examiner's withdrawal of the rejection of claims 1, 2, 6, 9, and 10 over WO 93/24149. According to the Examiner, Applicants' Reply of August 12, 2002, "obviates the anticipation of the instant invention" (Office Action at page 3).

IV. Claims 1, 2, 6, 9, 13-17, and 18-20 are not rendered obvious by WO 93/24149 in view of WO 90/09780

The Examiner rejects claims 1, 2, 6, 9, 13-17, and 18-20 under 35 U.S.C. § 103(a) in light of the combination of WO 93/24149 and WO 90/09780. According to the Examiner, WO 93/24149 "discloses a powder composition containing HPMC, ***chitosan***, and a medicament," which powder can be applied

"to the nasal mucosa" (Office Action at page 2; emphasis added). The Examiner acknowledges that WO 93/24149 "does not teach the instant cationic polymer," *i.e.*, aminoalkymethacrylate (page 2).

The Examiner alleges that "it would have been obvious" to substitute the chitosan of WO 93/24149's powder composition with the "co-polymethylacrylates" of WO 90/09780, since the reference allegedly teaches "the equivalency of chitosan and the polymethacrylates" (page 3). Thus, the Examiner urges that the skilled artisan would have been motivated to effect such a replacement, with an expectation of similar results, "since both chitosan and polymethacrylates are polycationic substances that improve the formulation as taught by WO 90/09780" (*id*).

The Examiner "relies on the secondary reference to teach the equivalence between the cationic polymer used in WO 93/24149 and the instant polymers" (page 4). He also states that "the applicant has not provided any unexpected results using the instant polymers. Therefore, the claims are rejected as *prima facie* obvious" (*id*).

Applicants respectfully disagree, however, because

1. their application documents such unexpected results;

2. copolymethacrylates are not fungible and, in particular, the HPMA copolymethacrylate of WO 90/09780 is not equivalent to the claimed aminoalkylmethacrylate;

3. neither prior art reference teaches aminoalkylmethacrylate copolymers that can be used to improve the absorption of a medicine of high molecular weight beyond a rate that is possible with chitosan or DEAE-dextran; and

4. although the objective advanced by WO 93/24149 is the use of chitosan to "provide a sustained-release powdery pharmaceutical composition" (page 2, third full paragraph), the aminoalkylmethacrylate copolymer of the presently

claimed invention is not used to enhance or confer "sustained-release" of a drug.

1. ***The present application describes an unexpected improvement in the absorption of high molecular weight medicines that are formulated with an aminoalkylmethacrylate copolymer***

Contrary to the Examiner's allegation, the present application *does* provide unexpected results. Indeed, Applicants demonstrated that their aminoalkylmethacrylate copolymer, *e.g.,* Eudragit E100, has an "absorption promoting effect" that is "**superior** to the effect of poly-L-arginine, DEAE-dextran and chitosan." See "Experimental Example 7" at page 30 of the specification, and particularly lines 3-5 of page 31. *See* also Experimental Examples 3, 7, 8, 9, and 11, from which Applicants provide the following excerpts:

> *"It was found that Eudragit E100 has a better absorption-promoting effect than poly-L-arginine"*
> --Experimental Example 3, p.23.

> *"It was found that Eudragit E100 remarkably promotes the adsorption of G-CSF through nasal mucosa"*
> --Experimental Example 6, p.27.

> *"It was found that Eudragit E100 remarkably promotes the pernasal absorption of growth hormone. The absorption rate for the case where Eudragit E100 was added was 10 times higher than the ratio for the absence of Eudragit E100"*
> --Experimental Example 10, p.40.

All such findings, as disclosed, underscore Applicants' surprising discovery that the claimed composition is able to increase the rate at which high molecular weight medicines are absorbed through a mucosal membrane, beyond what is possible with drug formulations comprising chitosan or DEAE-dextran, per WO 90/09780.

The person of ordinary skill in the art would not have expected the substitution of chitosan or DEAE-dextran with a copolymethacrylate of WO

93/24149, to boost the absorption rate of medicines, let alone to improve the absorption rate of high molecular weight medicines through a nasal lining. This fact alone belies the Examiner's stated position on point. Applicants also have appended additional data to illustrate the superior mucosal absorption properties of preparations containing the aminoalkylmethacrylate copolymer, Eudragit E100.

In short, drugs can be absorbed through the mucosa via the paracellular or the intercellular space of a "tight junction" of mucosal tissue. It is via the latter route that Applicants consider to be important for the absorption of high molecular weight and hydrophillic medicines through mucosa.

"Experiment 1" shows, as do the Experimental Examples in the application, that the aminoalkylmethacrylate copolymer, Eudragit E100 is approximately 10-times superior in its ability to transport substances through the intercellular space than DEAE-dextran, chitosan, or poly-L-arginine.

"Experiment 2" illustrates that the aminoalkylmethacrylate copolymer is approximately 100-times better at enhancing the transmission of G-CSF through the mucosal intercellular space, than DEAE-dextran, chitosan, or poly-L-arginine.

2. ***Copolymethacrylates are not fungible***

The Examiner considers the copolymethacrylates of WO 90/09780 to be equivalent to the chitosan of WO 93/24149. However, the Examiner failed to realize that not all copolymethacrylates are fungible, *i.e.*, interchangeable.

From reading WO 90/09780, the person of ordinary skill in the art would have understood that a copolymethacrylate, such as "HPMA" disclosed at page 5 of WO 90/09780, could be used as the "polycationic substance," instead of the preferred DEAE-dextran or chitosan. There is no guidance in WO 90/09780 as to what kinds of copolymethacrylates could be used to improve the mucosal absorption of high molecular weight medicines. In fact, the copolymethacrylate examples given in WO 90/09780 teach away from preparing a powdered

preparation of a high molecular weight medicine with an aminoalkylmethacrylate copolymer as is presently claimed.

Specifically:

(i) HPMA (N-(2-hydroxypropyl)methacrylamide) copolymers, exemplified at page 5 of WO 90/09780, are not equivalent to the claimed aminoalkylmethacrylate

HPMA, (N-(2-hydroxypropyl)methacrylamide), is different to the aminoalkylmethacrylate copolymer of the present invention. HPMA is an amide and, unlike an aminoalkylmethacrylate copolymer, is therefore not cationic. Furthermore, it has long been established that HPMA is useful for sustaining drug release and reducing the toxicity of drugs to which it is conjugated. See, for example, the abstract of Seymour *et al.*, *The pharmacokinetics of polymer-bound adriamycin*, Biochem Pharmacol., 15;39(6):1125-31,1990, which relates the findings of an adriamycin(ADR)/HPMA copolymer. The authors conclude that "the circulating half-life of HPMA copolymer-ADR was approximately 15 times longer than that of the free drug." Similarly, see the abstract of Caiolfa *et al.*, *Polymer-bound camptothecin: initial biodistribution and antitumour activity studies*, J. Control. Release, 65(1-2):105-19, 2000, which concludes that HPMA-camptothecin conjugate can contribute to the "prolonged intra-tumor retention and sustained release of the active drug."

Accordingly, HPMA copolymers are not examples of copolymethacrylates that improve the rate of absorption of a high molecular weight medicine through a mucosal membrane. Quite the opposite is true. HPMA copolymers retain drugs in a certain vincinity, and *maintain* a certain rate of release of a drug to which it is bound.

Thus, aminoalkylmethacrylate and HPMA copolymers are not fungible. The person of ordinary skill would not expect, after substituting the chitosan of WO 93/24149 with the HPMA copolymer of WO 90/09780, to arrive at Applicants' claimed invention.

Furthermore, nowhere does WO 90/09780 teach, or provide guidance, as to other suitable copolymethacrylates that could be used instead of DEAE-dextran or chitosan. The only other methacrylate copolymer, "Eudragit L," disclosed at page 9 of WO 90/09780, is used in drug formulations that are to be delivered to the colon. Eudragit L is not an aminoalkylmethacrylate copolymer, and cannot be used as a cationic polymer as prescribed by the presently claimed invention. The person of ordinary skill would not have substituted chitosan with Eudragit L and expected to obtain the surprising results documented in the present application.

Thus, the term "co-polymethacrylate," in WO 90/09780, encompasses a variety of methacrylate copolymers that exhibit different characteristics, of which, aminoalkylmethacrylate copolymers are a subgenera that is neither taught nor suggested by either of the prior art references.

(ii) The objective of WO 93/24149 is to provide sustained release of a drug, not to improve the absorption rate of high molecular weight medicines

Finally, the aim of WO 93/24149 is to "provide a sustained-release powdery pharmaceutical composition with improved adhesion characteristics which provides a high availability of the active ingredient" (page 2, last paragraph). That pharmaceutical composition comprises non-ionic cellulose ether derivative (including hydroxypropylmethyl cellulose), and a chitin-derived polymer (*e.g.*, chitosan). The "improved adhesive characteristics" (emphasis added) in WO 93/24149 is imparted by, for instance, chitosan.

Accordingly, the objective of WO 93/24149 does not entail improving the rate of absorption of high molecular weight medicines through a mucosal membrane. Rather, its objective is to make the "active ingredient" highly available, via improved *adhesion*. Thus, the person of ordinary skill in the art, could substitute the chitosan of WO 93/24149 with another polycationic polymer in order to accomplish this same effect. The skilled artisan would not have been motivated, however, to replace the chitosan of the powdery

pharmaceutical composition with the claimed aminoalkylmethacrylate copolymer; this, because (a) neither reference even suggests that aminoalkylmethacrylate copolymers can be used in such compositions, (b) the copolymethacrylates that are described in WO 90/09780 function differently to, and have different properties to, the aminoalkylmethacrylate copolymer presently claimed, and (c) the aminoalkylmethacrylate copolymers improve the rate at which high molecular weight drugs are absorbed through mucosal membranes. The latter enhancing effect is not taught or suggested in any of the cited references.

Accordingly, the presently claimed invention is not obvious over WO 93/24149 in view of WO 90/09780, and Applicants respectfully request that the Examiner withdraw this rejection.

V. Claims 1, 2, 7, 9, 13-17, and 19-20 are not unpatentable under 35 U.S.C. § 103(a) in view of WO 90/09780

The Examiner states that "it would have been obvious to one of ordinary skill in the art to use any of the suitable cationic polymers taught by WO 90/09780 with the reasonable expectation of similar results since the reference suggests the use of several interchangeable polycationic substances" (Office Action, page 4).

Applicants disagree with the Examiner's rationale for rejecting these claims. As Applicants have explained in detail above, the polycationic substances disclosed in WO 90/09780, do not teach methacrylate copolymers that are equivalent to the presently claimed aminoalkylmethacrylate copolymers.

The Examiner states that "if the prior art structure is capable of performing the intended use, then it meets the claim" (Office Action at page 5). Applicants have shown that the prior art polymethacrylates could not be used in the fashion prescribed by the claimed invention. Accordingly, for these reasons, and for the reasons elaborated upon in section IV above, Applicants respectfully request that the Examiner withdraw this rejection.

VII. Claim 8 is not obvious over WO 93/24149 in view of WO 90/09780 in further view of JP 406065090 *or* WO 90/09780 in view of JP 406065090

The Examiner states that it would have been obvious to incorporate the G-CSF of JP 406065090 into either WO 93/24149 or WO 90/09780, since "JP teaches the instant protein is suitable for nasal administration."

Since Applicants already have explained in detail why the claimed aminoalkylmethacrylate copolymer preparation is non-obviousness, the Examiner's rejection is not applicable. Nevertheless, Applicants refer the Examiner to Experimental Example 8, at page 33 of the application, where Applicants revealed that Eudragit E100 was better than poly-L-arginine, chitosan, and DEAE-dextran in promoting absorption of G-CSF through the nasal mucosa.

Accordingly, the use of aminoalkylmethacrylate copolymers, such as Eudragit E100, in powdered preparations is superior to other polycationic polymers of the prior art in increasing the absorption rate of high molecular weight medicines. According to Experimental Example 8, and in Applicants' comments in section IV above, one would not have expected to obtain an increased absorption of G-CSF in either of WO 93/24149 or WO 90/09780. Rather, one would have expected the formulations of the latter prior art to retain G-CSF in the nasal mucosa, and exhibit a sustained-release profile.

For at least these reasons, Applicants respectfully request that the Examiner withdraw this rejection.

VIII. Claim 18 is not obvious over WO 93/24149 in view of WO 90/09780 in further view of Stanton *et al.* (USP 5,807,552) *or* WO 90/09780 in view of Stanton *et al.* (USP 5,807,552)

The Examiner alleges that it would have been obvious to "incorporate hapten-carrier (protein) molecules in WO's composition to illicit immune

response and function as a vaccine as taught by Stanton *et al.* One would be motivated to incorporate a specific medicine depending on the symptoms to be treated."

Since Applicants have demonstrated the non-obviousness of the claimed powdered preparation, the Examiner's rejection is obviated. Accordingly, Applicants respectfully request that the Examiner withdraw this rejection.

IX Conclusion

In view of the foregoing amendments and remarks, applicants respectfully request favorable reconsideration and allowance of the pending claims. If there are any issues remaining which the examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the examiner is hereby respectfully invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,

Date: 24 April 2003

By: S. A. Bent

FOLEY & LARDNER
Washington Harbour
3000 K Street, N.W., Suite 500
Washington, D.C. 20007-5109
Telephone: (202) 672-5404
Facsimile: (202) 672-5399

Stephen A. Bent
Attorney for Applicants
Registration No. 29,768

MARKED-UP VERSION OF THE CLAIMS

1. (Once amended) A preparation in powder form for administration through mucosa, comprising a medicine of high molecular weight and aminoalkylmethacrylate copolymer[or polyvinyl acetal diethylaminoacetate].

13. (Once amended) The preparation of claim 1, which comprises 0.1 to 90 w/w% of aminoalkylmethacrylate copolymer[or polyvinyl acetal diethylaminoacetate].

14. (Once amended) The preparation of claim 1, which comprises 1 to 50 w/w% of aminoalkylmethacrylate copolymer[or polyvinyl acetal diethylaminoacetate].

Reference 1

The effect of various transmission-enhancing agent on in vitro transmission through membrane of substances using Caco-2 as a model membrane is examined.

Experiment 1. The effect of various transmission-enhancing agent on transmission of mannitol, which is a marker passing through intercellular space

concentration of	transmission coefficient (cm/s)			
agent (%)	Eudragit E-100	DEAE-Dextran	Chitosan	Poly-L-Arginine
0.000	2.1E-07	2.1E-07	2.1E-07	2.1E-07
0.001	2.4E-07	-	-	-
0.005	5.8E-06	-	-	-
0.010	2.3E-05	-	-	-
0.050	3.6E-05	-	-	-
0.100	3.2E-05	2.6E-07	3.4E-07	9.4E-07
0.500	3.8E-05	2.3E-07	8.3E-07	1.9E-06
1.000	3.5E-05	2.5E-07	5.1E-07	2.5E-06
5.000	3.0E-05	1.6E-06	2.9E-06	5.7E-06

note: 2.1E-07 means 2.1×10^{-7}.

Experiment 2. The effect of various transmission-enhancing agent on transmission of G-CSF

concentration of	transmission coefficient (cm/s)			
agent (%)	Eudragit E-100	DEAE-Dextran	Chitosan	Poly-L-Arginine
0.000	<5.0E-08	<5.0E-08	<5.0E-08	<5.0E-08
0.010	5.2E-07	<5.0E-08	<5.0E-08	<5.0E-08
0.050	2.4E-06	<5.0E-08	<5.0E-08	<5.0E-08
0.100	2.9E-06	<5.0E-08	<5.0E-08	<5.0E-08
0.500	4.1E-06	<5.0E-08	<5.0E-08	<5.0E-08
1.000	3.8E-06	<5.0E-08	<5.0E-08	<5.0E-08

note: <5.0E-08 means "below 5.0×10^{-8}", which is lower limit of determination.